Zika Virus in the Americas: An HHS Expert Consultation to Accelerate the Development of Countermeasures

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Regulatory Considerations: Developing Drugs for Use in Pregnant Women

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Disclaimer

The views expressed in this presentation are my own and do not necessarily reflect those of the Food and Drug Administration.

Outline

- Designing a clinical development program to support a U.S. marketing application (and relevant regulations)
- Considerations for including pregnant women in clinical trials
- Review of New Drug Applications (NDA) and Biologics License Applications (BLAs) submitted to Center for Drug Evaluation and Research (CDER)
- Expedited programs for serious conditions
- Useful Resources

Clinical Development Programs – General Concepts

Marketing Authorization
FDA's Considerations

- Under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof:
  - Can conclude there is **substantial evidence** that the drug will have the effect it purports or is represented to have
  - Has determined that the drug is **safe for use** (balancing benefit and risk)

- The methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are adequate to preserve its **identity, strength, quality, and purity.**

- The labeling is not false nor misleading.

21 USC § 355(d) (Federal Food, Drug, and Cosmetic Act)

"Substantial Evidence" Defined

Evidence consisting of adequate and well-controlled investigation**s**, including clinical investigation**s**, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

21 U.S.C. § 355(d), FD&C Act Section 505(d)

Goal of Clinical Development

Chemistry, Manufacturing, & Controls

21 CFR 312.23(a)(7)

- To assure identity, strength, quality, and purity of the drug substance and drug product

Non-Clinical

21 CFR 312.23(a)(8)

- To assure that it is reasonably safe to conduct the proposed clinical investigations.

Clinical

21 CFR 314.126

- The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.
- Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs.

Developing Drugs for Use in Pregnant Women

General Considerations for Study Design

Dosing selection, eligibility criteria, and trial design should be informed by:

- Nonclinical data, especially genotoxicity, female reproduction and embryo-fetal toxicity studies
- Clinical data in non-pregnant women
- Placental transfer studies (in vitro, explants of human placenta, animal placental perfusion models)
- Clinical pharmacology data (pharmacokinetics and pharmacodynamics) during pregnancy
- Ethical considerations (studies should not be conducted if there is no anticipated use during pregnancy or if fetal risk is known or highly suspected)

Sheffield et al. Designing Drug Trials: Considerations for Pregnant Women. Clin Infect Dis. 2014;59 Suppl 7:S437-44.

Physiologic Changes in Pregnancy Affect PK/PD Parameters

Absorption	• Nausea/vomiting in early pregnancy • Rise in progesterone → delayed gastric emptying and prolonged gastric transit time
Distribution	• 30-50% increase in cardiac output, starting in 1st trimester • 40-50% increase in blood volume by 3rd trimester • Decreased albumin (diminished protein-binding)
Metabolism	• Changes in activities of CYP450 enzymes (e.g., ↑ CYP2A6, ↓ CYP 1A2)
Excretion	• Increased renal blood flow; 50% increase in glomerular filtration rate • Increased clearance of renally-excreted drugs

Sheffield et al. Designing Drug Trials: Considerations for Pregnant Women. Clin Infect Dis. 2014;59 Suppl 7:S437-44.

If a Drug Candidate Has been Chosen…

Is it an FDA-approved product?

YES

- **Nonclinical toxicology data are available**
- **Clinical experience in non-pregnant women may be available**
- **Pregnancy exposure registry may be available to support safety**
- **Are there PK data to ensure adequate systemic exposure in pregnancy?**

NO

- **Are nonclinical reproductive and developmental toxicity studies complete/adequate?**
- **Are there concerning findings in these nonclinical studies?**
- **Are there effective alternative therapies?**
- **Risk/benefit consideration for mother and fetus?**

Participation of Pregnant Women in Clinical trials

- Design of clinical programs should take into account the indication(s) being pursued
- Two possible scenarios:
  - Women becoming pregnant during a clinical trial (e.g., developing a treatment for symptoms associated with Zika infection)
  - Clinical trials aiming specifically to enroll pregnant women (e.g., developing a treatment to reduce the risk of developing congenital anomalies associated with Zika infection during pregnancy)

Protocol Considerations: Design Issues Related to Efficacy

- FDA is available for Pre-IND consultation and will provide guidance under the IND review process.
- Study protocols should outline:
  - Study design – randomization, blinding, control group (vs. placebo, active treatment, historical control)
  - Rationale for dose selection
  - Inclusion/exclusion criteria
  - Efficacy endpoint(s)
  - Justification for sample size
  - Statistical analysis plan

Investigational New Drug Application:
http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm

Protocol Considerations: Obtaining Useful Safety Data

Study endpoints and mechanisms of data collection should enable assessment of maternal, fetal, and neonatal outcomes of interest by capturing the following:

- Background prevalence of adverse pregnancy outcomes
- Accurate pregnancy dating (ultrasound reports)
- Timing of exposure to drug
- Extent of exposure to drug (dose/duration)
- Variability of response
- Documented pregnancy outcomes:
  - Gestational age at delivery
  - Results of prenatal testing, if done
  - Birth defects identified – major and minor
  - Any complications – maternal, neonatal

CDER's Review of Marketing Applications

Review of NDAs and BLAs: Process

Standard Review Clock (6 months for Priority Review, not shown)

CDER 21st Century Review Process
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.htm

Decision-Making: Structured Approach to Benefit-Risk Assessment

- Analysis of Condition
- Current Treatment Options
- Benefit
- Risk
- Risk Management

21 USC § 355(d) & Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making
http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM329758.pdf

Expedited Programs: When the Stakes are High

Expedited Programs for Serious Conditions

Four FDA programs are intended to facilitate and expedite development and review of new drugs to address **unmet medical need** in the treatment of a **serious or life- threatening** condition.

Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

Expedited Programs for Serious Conditions

Fast Track

Nonclinical or clinical data demonstrate the potential to address unmet need

Breakthrough Therapy

Preliminary clinical evidence of substantial improvement over available therapies

Priority Review

Provide significant improvement in safety or effectiveness

Accelerated Approval

Meaningful advantage over available therapy using surrogate endpoint

Resources

- Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf

- Expedited Programs for Serious Conditions – Drugs and Biologics

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

- CDER 21st Century Review Process Desk Reference Guide

http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.htm

- 5 Things to Know About the New Drug Approval Process

http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM487830.wmv

Resources

- Evaluating the Risks of Drug Exposure in Human Pregnancies
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071645.pdf

- Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425398.pdf

- Establishing Pregnancy Exposure Registries
http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133332.pdf

- Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072133.pdf

Resources

- Reproductive and Developmental Toxicities — Integrating Study Results to Assess Concerns

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079240.pdf

- List of Pregnancy Exposure Registries (maintained by FDA's Office of Women's Health)

http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm